Role of vagal C-fiber afferents in the bronchomotor response to lactic acid in the newborn dog

MONICA J. MARANTZ, SANDRA G. VINCENT, AND JOHN T. FISHER
Departments of Physiology, Paediatrics, and Anaesthesiology, Queen’s University, Kingston, Ontario, Canada K7L 3N6

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Marantz, Monica J., Sandra G. Vincent, and John T. Fisher. Role of vagal C-fiber afferents in the bronchomotor response to lactic acid in the newborn dog. J Appl Physiol 90: 2311–2318, 2001.—We addressed the hypothesis that vagal C-fiber afferents and cyclooxygenase products are the mechanisms responsible for lactic acid (LA)-induced bronchoconstriction in the newborn dog. Perineural capsaicin and indomethacin were used to block conduction of vagal C fibers and production of cyclooxygenase products, respectively. Perineural capsaicin eliminated (85%) the increase in lung resistance (Rt; 45 ± 5.6%) due to capsaicin (25 μg/kg), whereas the increase in Rt (54 ± 6.9%) due to LA (0.4 mmol/kg) was only inhibited by 37 ± 4.7% (P < 0.05). Atropine reduced LA-induced bronchoconstriction (42 ± 2.1%) by an amount similar to that obtained with perineural capsaicin. However, inhibition was significantly increased when atropine was combined with indomethacin (61 ± 2.7%; P < 0.05), implicating cyclooxygenase products in the LA-induced bronchoconstrictor response. We conclude that the mechanisms responsible for LA-induced bronchoconstriction in the newborn are 1) activation of vagal C-fibers, which, through projections to medullary respiratory centers, leads to activation of vagal cholinergic efferents; 2) production of cyclooxygenase products, which cause bronchoconstriction independent of medullary involvement; and 3) an unknown bronchoconstrictor mechanism, putatively tachykinin mediated. On the basis of our data, pharmaceutical targeting of pulmonary afferents would prevent multiple downstream mechanisms that lead to airway narrowing due to inflammatory lung disease.

Myelinated afferents undergo considerable postnatal maturation (8) that is accompanied by alterations in respiratory reflex responses. In contrast, the role of lung C-fiber afferents in the control of airway caliber, pattern of breathing, lung pathologies, or inflammation in the neonate remains largely unstudied (7, 8). Successful delivery and survival of premature infants have meant that associated inflammatory lung disease would lead to activation of C-fiber afferents (13). Furthermore, the transition to air breathing is an inherently unstable period that is accompanied by hypoxemia and acidosis (10, 16), factors that may activate C-fiber afferents. Interestingly, vagal innervation appears to be critical in the transition at birth (31), and the newborn in general has been suggested to be particularly sensitive to vagal afferent feedback (10, 20, 31).

Activation of C-fiber receptors with capsaicin causes reflex narrowing of airway caliber in the newborn (1), which is blocked by capsazepine, a specific antagonist of the capsaicin or vanilloid receptor (3, 21). Lactic acid (LA), an endogenous stimulant of C-fibers in the adult (18), causes bronchoconstriction in the newborn that is unaffected by capsazepine, suggesting a non-vanilloid receptor 1 mechanism (21). We concluded that LA acted via activation of pulmonary C-fibers and muscarinic efferents, although this was an assumption based on previous work in the adult (18) and not directly tested. It is possible that chemoreflex pathways contributed to the LA response, similar to that shown for hypercapnia (30). Finally, Nault and co-workers (21) observed an atropine resistant component of the LA-induced bronchoconstriction that was not explored.

The present study was designed to define the mechanisms responsible for LA-induced bronchoconstriction of the newborn. More specifically, we investigated the role of pulmonary C-fiber afferents in the response, determined whether chemoreceptor afferents contribute to the reflex bronchoconstriction, and determined the origin of LA-induced bronchoconstriction that was atropine resistant.

METHODS

Experiments were performed on 28 mongrel dogs [age 1–13 days (mean = 6 ± 0.6 days) and body weight 465–1400 g (mean = 819 ± 55 g)]. Animals were anesthetized with an intraperitoneal injection of chloralose (75–100 mg/kg) and urethane (0.75–1.0 g/kg), and supplemental anesthesia (125 mg/kg urethane and 12.5 mg/kg chloralose) was administered intravenously at ~1-h intervals to maintain abolition of the withdrawal reflex and acute changes in blood pressure and heart rate. All experimental procedures conformed to the guidelines of the Canadian Council on Animal Care and were approved by the Queen’s University Animal Care Committee. Electrocardiogram was monitored via needle electrodes connected to a preamplifier, an oscilloscope, and an audio...
speaker. A tracheal cannula was inserted just below the larynx via a tracheotomy, and animals were ventilated with 40% O2–balance N2 at a ventilator frequency ranging from 33 to 43 breaths/min and tidal volumes of 6–10 ml/kg. Ventilator frequency and tidal volume were adjusted to provide normal arterial blood gases (blood gases; pH = 7.40 ± 0.01, arterial PCO2 = 37.5 ± 1.9 Torr, arterial PO2 = 192.7 ± 52 Torr) and resulted in tidal pressure swings of ~5 cmH2O transpulmonary pressure (Ptp). A cannula was placed in the right heart (placement checked postmortem) via the external jugular for capsaicin, ACh, and LA injections. Cannulas were placed in the femoral vein for administration of atropine and supplemental anesthesia and in the femoral artery for blood-gas sampling and arterial blood pressure measurement. The chest wall was opened at the xiphoid so that the pressure measured from the tracheal cannula represented Ptp during inspiration. Ptp was measured via a differential pressure transducer (±50 cmH2O; model MP45, Validyne) connected to the side port of the tracheal cannula. An end-expiratory load of 2–3 cmH2O was established to provide a normal functional residual capacity (9). Core temperature was maintained at 37°C with a servo-controlled heating blanket (animal blanket control unit model 50-6956, Harvard Apparatus). Animals were placed in a body plethysmograph, and respiratory flow was measured with a pneumotachograph (model 8300, Hans Rudolph) connected to a differential pressure transducer (Validyne MP45, ±2 cmH2O). Flow, electrocardiogram, blood pressure, and Ptp were acquired with a computerized chart recorder data acquisition package (CODAS, DATAQ Instruments, Akron, OH).

**Analysis of Pulmonary Mechanics**

Ptp and respiratory flow were acquired on-line by an additional computer (Zenith 151, Data Translation DT-2801-A) at a sampling frequency of 100 samples/s per channel for breath-by-breath calculations of inspiratory lung resistance (Ri; cmH2O·ml−1·s) and dynamic lung compliance (Cdyn,i; ml/cmH2O). Mean inspiratory Ri was calculated by dividing the mean pressure required to overcome the flow- resistive properties of the lung by the mean inspiratory flow. Cdyn,i was calculated by dividing the tidal volume by the Ptp swing between points of zero flow during inspiration. Dynamic lung elastance (Edyn,l) was calculated as the reciprocal of Cdyn,i.

**Protocols**

**Effects of perineural capsaicin treatment on the response to capsaicin and LA.** To assess the role of vagal C-fiber afferents in capsaicin and LA-induced bronchoconstriction, a solution of capsaicin was applied to the vagi (n = 8) to block C-fiber conduction. Before the animals were placed in the plethysmograph, the vagus nerves were isolated from the carotid artery and separated from surrounding tissue by a sheet of paraffilm to which catheters were attached.

The protocol consisted of five trials separated by 15 min. Each trial was initiated by an inflation to 20 cmH2O to maintain a constant volume history. Two minutes after the inflation, an 8-min data acquisition period began. The first trial consisted of a saline and ACh control in which 0.4 ml of saline was injected at 30 s into the acquisition period followed by an injection of ACh (20 μg/kg) at 3 min. In the second and third trials, capsaicin (25 μg/kg in 0.2 ml) and LA (0.4 mmol/kg in 0.4 ml) were injected at 30 s, respectively. After the third trial, a 1-ml solution of capsaicin (1% capsaicin dissolved in 90% mineral oil and 10% Tween 80) was infused through the catheters secured near the vagus nerves so that the exposed sections of the nerves were bathed in capsaicin solution. Forty-five minutes after perineural capsaicin treatment, the responses to capsaicin and LA after treatment were measured by repeating the capsaicin and LA trials.

**Effect of carotid body denervation on LA-induced bronchoconstriction.** To study the role of the carotid chemoreceptors in LA-induced bronchoconstriction, carotid bodies were surgically removed before capsaicin and LA injection (n = 3). Carotid bodies were located rostral to the hypoglossal nerve at the bifurcation of the carotid artery and removed by blunt dissection. All other aspects of the experimental setup remained the same. The magnitude of the bronchoconstriction resulting from LA injection in these animals was compared with the bronchoconstriction elicited in intact animals.

**Effect of atropine and indomethacin on LA-induced bronchoconstriction.** These experiments compared the effect of atropine alone with that of atropine plus indomethacin on the bronchoconstriction induced by LA. The protocol for these experiments consisted of the same trials as described in Effects of perineural capsaicin treatment on the response to capsaicin and LA (LA delivered in a volume of 0.8 ml). After the third trial, atropine (2 mg/kg, n = 4) or atropine followed 2 min later by indomethacin (15 mg/kg, n = 6) was injected into the femoral vein. The capsaicin and LA trials began 15 min after injection of atropine or indomethacin.

**Osmolarity and bronchomotor tone.** To assess a possible effect of osmolarity on bronchomotor tone, a comparison was made between the increases in Ri response to LA (0.4 mmol/kg) delivered in volumes of 0.4 ml (n = 7) and 0.8 ml (n = 7). An additional single study was done in which the change in Ri to injections of LA (0.4 mmol/kg) diluted to volumes of 0.4, 0.8, and 1.2 ml was compared before and after atropine (2 mg/kg).

**Drugs**

Chloralose (ICN Biochemicals) and urethane (Sigma Chemical) (0.25 and 2.5 g, respectively) were dissolved in 10 ml of heated saline. Anesthetic mixture was injected at an initial dose of 3–4 ml/kg with supplemental doses of 0.5 ml/kg. A stock solution of capsaicin was prepared by dissolving 10 mg capsaicin (Sigma Chemical) in a vehicle of 1 ml ethanol, 9 ml isotonic saline, and 2 drops Tween 80. ACh (Sigma Chemical) was dissolved in saline to a concentration of 200 μg/ml, and atropine (Sigma Chemical) was dissolved in saline to a concentration of 20 mg/ml. These solutions were then prepared daily for injection by dilution with saline to the desired concentration on the basis of the animal’s body weight. Injection volumes of all of these solutions was 0.2 ml. A stock solution of 3.3 M lactic acid [L-(+)-lactic acid, Sigma Chemical] was diluted with distilled H2O to the desired concentration for injection and injected in a volume of 0.4 or 0.8 ml. Indomethacin was prepared by dissolving the desired amount in 4–5 ml of a heated 5% sodium bicarbonate solution.

**Statistical Comparisons**

Baseline Ri and Edyn,l were calculated from the average of the 10 breaths prior to injection. The peak lung mechanics response for each animal was defined as the average between the two largest consecutive values after challenge. Ri response latency was defined as the time from injection to the onset of a maintained or continual increase in Ri above baseline. Percent inhibition of the change in Ri (ΔRi) response was calculated as [(control ΔRi response − test ΔRi response)/control ΔRi response] × 100. The time to peak was calculated as the time from jugular injection to the first
breath of the maximal response. Heart rate baselines were calculated as the average values over the 10 s preceding injections. Bradycardia was calculated as the lowest instantaneous heart rate after injection. Statistical comparisons were based on one-way ANOVA and paired t-test or unpaired t-test. A significant difference was defined as \( P < 0.05 \). All results are expressed as means ± SE unless otherwise indicated.

**RESULTS**

Table 1 and 2 contain the baseline values for lung mechanics for each series of experiments. Table 3 presents capsaicin and LA responses in terms of response latencies and time to peak RL. Table 4 presents capsaicin and LA responses in terms of response latencies and time to peak RL. Figure 1 illustrates the response of RL and Edyn,L for a typical animal to right heart injection of either capsaicin or LA compared with intact (\( P > 0.05 \), consistent with the response being primarily or partially mediated by vagal afferent C fibers. The bronchoconstrictor response to right heart injection of capsaicin was almost totally abrogated (Figs. 2 and 3). In contrast, the response to LA injection, although reduced, still resulted in a significant increase in RL (Figs. 2 and 3), suggesting that an additional mechanism contributes to this response. To test whether part of the remaining bronchoconstrictor response reflected activation of peripheral chemoreceptors by LA, we performed right heart injections of LA in three newborns in which carotid body denervation was performed before injection. Carotid body denervation had no apparent effect on the bronchoconstrictor response (Fig. 4; \( P > 0.05 \)).

**Osmolarity.** We found no difference in the bronchoconstrictor response to LA dissolved in 0.4 and 0.8 ml (\( P > 0.05 \)), which correspond to osmolarities of 1,150 (range 590–1,580) and 472 (range 330–700) mosM, respectively. Furthermore, regression analysis of osmolarity vs. percent change or absolute change in RL failed to reveal a relationship between the two variables (\( P > 0.05 \); data not shown). In a single experiment, we injected 0.4 mmol/kg of LA dissolved in volumes of 0.4, 0.8, and 1.2 ml distilled water, which corresponds to osmolarities of 1,350, 615, and 370 mosM, respectively. All three LA injections elicited a similar percent change of RL in the intact animal (\( P > 0.05 \)), as did the atropine-resistant component (\( P > 0.05 \)).

**Effects of atropine and indomethacin on the response of RL to LA.** Atropine treatment alone resulted in a decrease of the peak change in RL from 60 ± 13% in intact animals to 41 ± 8.5% after treatment (Fig. 5, A and B). The degree of inhibition produced by blockade of cholinergic efferents is similar in magnitude (\( P > 0.05 \)) to that produced by blockade of C-fiber afferents (Fig. 3B), illustrating that the vagally mediated reflex component of the LA-induced bronchoconstriction can be detected by blocking the efferent or afferent arm of the central reflex. Nevertheless, the bronchoconstrictor

### Table 1. Baseline values of lung mechanics

<table>
<thead>
<tr>
<th>Protocol</th>
<th>( n )</th>
<th>( \text{RL}_{\text{intact}} ) cmH(_2)O·ml(^{-1})·s(^{-1} )</th>
<th>( \text{Edyn}_{\text{intact}} ) cmH(_2)O/ml</th>
<th>( \text{RL}_{\text{after treatment}} ) cmH(_2)O·ml(^{-1})·s(^{-1} )</th>
<th>( \text{Edyn}_{\text{after treatment}} ) cmH(_2)O/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>12</td>
<td>0.056 ± 0.01</td>
<td>0.557 ± 0.03</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>6</td>
<td>0.054 ± 0.01</td>
<td>0.518 ± 0.05</td>
<td>0.061 ± 0.01</td>
<td>0.531 ± 0.04</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>5</td>
<td>0.063 ± 0.01</td>
<td>0.568 ± 0.074</td>
<td>0.066 ± 0.01</td>
<td>0.575 ± 0.072</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n \), no. of dogs. \( \text{RL} \), lung resistance; \( \text{Edyn} \), dynamic lung elastance; NA, not applicable. There were no significant differences.

### Table 2. Baseline values of lung mechanics

<table>
<thead>
<tr>
<th>Protocol</th>
<th>( n )</th>
<th>( \text{RL}_{\text{intact}} ) cmH(_2)O·ml(^{-1})·s(^{-1} )</th>
<th>( \text{Edyn}_{\text{intact}} ) cmH(_2)O/ml</th>
<th>( \text{RL}_{\text{after treatment}} ) cmH(_2)O·ml(^{-1})·s(^{-1} )</th>
<th>( \text{Edyn}_{\text{after treatment}} ) cmH(_2)O/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>4</td>
<td>0.076 ± 0.01</td>
<td>0.602 ± 0.02</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lactic acid 1</td>
<td>4</td>
<td>0.078 ± 0.01</td>
<td>0.611 ± 0.02</td>
<td>0.071 ± 0.01</td>
<td>0.625 ± 0.04</td>
</tr>
<tr>
<td>Saline</td>
<td>6</td>
<td>0.072 ± 0.01</td>
<td>0.596 ± 0.04</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lactic acid 2</td>
<td>6</td>
<td>0.078 ± 0.01*</td>
<td>0.573 ± 0.03</td>
<td>0.066 ± 0.01*†</td>
<td>0.569 ± 0.04</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n \), no. of dogs. * Different from saline control, \( P < 0.05 \). † Different from intact, \( P < 0.05 \).
response remaining after muscarinic-receptor blockade shows that a large portion of the LA-induced bronchoconstrictor response is not mediated by cholinergic efferents.

The effect of atropine plus indomethacin on the average breath-by-breath change in Rl in response to LA is shown in Fig. 5 (A and B). Combined treatment further reduced the LA response compared with that seen with atropine alone ($P < 0.05$), reducing the peak increase in Rl from $47 \pm 7.8\%$ intact to $23 \pm 3.5\%$ after treatment. The magnitude of the inhibition (Fig. 5C) seen with the combined atropine and indomethacin pretreatment suggests that the production of cyclooxygenase products plays a significant role in mediating the LA bronchoconstrictor response in the newborn dog. However, other factors also contribute to the LA response, because $40\%$ of the bronchoconstriction remained after pretreatment with atropine and indomethacin.

**DISCUSSION**

The present study was designed to identify the mechanisms responsible for the bronchoconstrictor response of the neonatal lung to LA. Our laboratory previously reported capsaicin- and LA-induced bronchoconstriction (21); however, questions remained regarding the mechanisms mediating these responses. In the present study, we describe two of the mechanisms that mediate LA-induced bronchoconstriction and implicate a third. Approximately $40\%$ of the bronchoconstrictor response to LA is mediated by a central reflex that consists of activation of vagal C-fiber afferents that projects to medullary respiratory centers, which subsequently cause activation of cholinergic efferents to airway smooth muscle (ASM). We also found that $60\%$ of the LA-induced bronchoconstriction is atropine resistant and that cyclooxygenase products are responsible for a significant component of this response.

**Perineural Capsaicin**

We relied on the application of perineural capsaicin to selectively block C-fiber afferents of the vagus nerve.
This was a key tool in the interpretation of our results, because it allowed us to definitively identify whether pulmonary C fibers contributed to the bronchoconstrictor responses. Jancso and Such (14) demonstrated that application of capsaicin to peripheral nerves blocked the reflex effects of capsaicin and phenyldiguanine, substances that evoke the classic pulmonary chemoreflex through activation of C fibers. The effectiveness of perineural capsaicin treatment in selectively blocking C-fiber afferents has been tested widely in studies of changes in reflex responses and alterations in the compound action potential. Perineural capsaicin treatment has no effect on reflexes dependent on myelinated afferents, such as the Hering-Breuer reflex (11, 17, 26),

Fig. 2. Effect of perineural capsaicin on the breath-by-breath response of lung mechanics to Caps and LA. Average breath-by-breath values of change (Δ) in Rₜ (top) and Edynₜ (bottom) from baseline values in response to right heart injections of Caps (25 μg/kg; left) and of LA (0.4 mmol/kg; right) before (●) and after (○) application of perineural capsaicin bilaterally to the vagus nerves are shown. Perineural capsaicin essentially abolished the response to Caps but only caused a reduction in the response to LA. Arrows indicate injection of Caps or LA.

Fig. 3. Average maximal increase in Rₜ and percent inhibition of Caps- and LA-induced bronchoconstriction by perineural capsaicin. Values are means ± SE. A: mean peak increase of Rₜ in response to Caps (25 μg/kg) and LA (0.4 mmol/kg) before (Intact) and after (Peri) bilateral application of perineural capsaicin. *Significantly different from the intact response, P < 0.05. **Significantly different from the Caps response after treatment, P < 0.05. B: mean percent inhibition of the peak Rₜ response to Caps and LA by treatment with perineural capsaicin. ***Significantly different from the Caps response, P < 0.01.
but it does eliminate C-fiber-related responses, such as the pulmonary chemoreflex evoked by capsaicin (11, 26). Recordings of the compound action potential in the vagus nerve before and after treatment demonstrate that perineural capsaicin abolishes the C wave, but it has little or no effect on the A wave of the capsaicin (11, 26). Particularly relevant to the present study is the use of the neurotoxic effects of capsaicin to abolish the C-fiber response to pulmonary edema in the newborn lamb (5). We paired LA trials with capsaicin in our study so that the abolition of the response to right heart injection of capsaicin served as an indicator of the loss of vagal C-fiber activity. Because the capsaicin response was eliminated after perineural capsaicin treatment (Figs. 2 and 3), we are confident in attributing the remaining response after injection of LA to mechanisms other than capsaicin-sensitive C-fiber afferents. Finally, the close agreement between the impact of perineural capsaicin or atropine on the reflex response to LA provides independent support for the effectiveness of perineural capsaicin (see below).

**LA Vagal Afferent and Efferent Mechanisms**

LA has been shown to activate C-fiber afferents in the adult rat (18), although the action of LA in the newborn does not appear to rely on the vanilloid receptor 1 of these afferents. Nault and co-workers (21) reported that LA induced a bronchomotor response that was "consistent" with a role for C-fiber afferents in the newborn, but they did not test this assumption. LA could have acted through chemoreceptor afferents or by causing the release of other bronchoactive components, although the current data do not support a role for peripheral chemoreceptors (30). In the present study, we established that C fibers contribute to the reflex bronchomotor response to LA, because perineural capsaicin reduced the response by ~40%. The failure of perineural capsaicin to eliminate the response also clearly implicates additional mechanisms. The role for C-fiber afferents in the LA response of the newborn is consistent with the excitatory effect of LA on C-fiber afferent endings and pattern of breathing for the adult rat (18). Our results differ from those of Lee et al. (18), in which the entire response to LA was abolished by perineural capsaicin. This apparent discrepancy could reflect species differences between the canine and rat model or differences between the adult and the neonate. In addition, reflex output was measured as pattern of breathing in the rat (i.e., respiratory muscle activation), whereas we measured reflex output in terms of lung mechanics in a ventilated animal (i.e., changes in ASM activation). Thus the apparent difference between the studies may reflect the relative contribution of C-fiber afferents to the two components of the reflex response.

Blockade of vagal cholinergic efferents, by the muscarinic antagonist atropine, reduced the LA-induced bronchoconstriction by an amount that was similar to that seen with perineural capsaicin. This provides an additional assessment, independent of perineural capsaicin, of the magnitude of the vagal reflex component associated with LA-induced bronchoconstriction. Approximately 60% of the LA-mediated increase in Rt. remained after atropine treatment, unlike the response to capsaicin (1). Several possible mechanisms could contribute to the remaining bronchoconstriction, including osmolarity of the LA solution, production of...
cyclooxygenase products, or release of tachykinins from C-fiber afferents.

Delivery of the same LA stimulus at widely varying osmolarities had no impact on the reflex response in the present study. Thus high osmolarity alone does not appear to be causing bronchoconstriction in our studies. However, the present study does differ from our laboratory’s previous findings (21), where the bronchoconstriction induced by LA delivered in a volume of 0.4 ml was more sensitive to atropine. The reason for this difference is not apparent because the protocols are very similar.

LA and Cyclooxygenase Products

Our atropine-indomethacin protocols implicate cyclooxygenase products in the atropine-insensitive component of the bronchoconstrictor response to LA. Although it is not possible from our data to identify which cyclooxygenase product(s) caused atropine-resistant bronchoconstriction in the newborn dog, two possible candidates are thromboxane A2 (TxA2) and/or PGE2. Both are major products of the cyclooxygenase pathway of arachidonic acid metabolism in canine airways (4). TxA2 exerts excitatory actions on ASM and is thought to play a major role in airway hyperresponsiveness (2) and contracts ASM (4). Furthermore, infusion of acid in the presence of stoichiometrically equal quantities of base stimulates the release of TxA2 in the cat (27). Dosages of PGE2 that are higher than those that cause smooth muscle relaxation (4) result in bronchoconstriction in the adult dog as a result of activation of C fibers (15, 25).

Approximately 40% of the response to LA remains after treatment with atropine and indomethacin. A potential mechanism is the release of tachykinins from pulmonary C fibers. Substance P and neurokinin A (NKA) cause ASM contraction through activation of the NK1 and NK2 receptors, respectively, but the degree to which tachykinins play a role in the modulation of airway tone varies greatly between species (see Refs. 24, 28, 29). In the adult dog, aerosolized NKA causes bronchoconstriction which is blocked by a NK2-receptor antagonist, whereas aerosolized SP had no effect on lung mechanics (28). Tachykinin-containing immunoreactive nerves are distributed in the pulmonary system of dogs (12, 22, 23), and tachykinins are released on exposure to numerous endogenous agents, including protons, in other species (19). Further experiments are required to determine whether the release of NKA from pulmonary C fibers is responsible for the residual bronchoconstrictor response that remained in our experiments after treatment with atropine and indomethacin.

In summary, the mechanisms responsible for LA-induced bronchoconstriction in the newborn consist of 1) a central reflex that originates with the activation of C-fiber afferents, central medullary integration of C-fiber input, and subsequent cholinergic vagal efferent activation, which accounts for ~40% of the bronchoconstrictor response; 2) a nonvagal peripheral mechanism
that is mediated by cyclooxygenase products (which is responsible for ~20% of the response); and 3) an unidentified component that is also peripheral in nature, possibly due to the release of tachykinins from pulmonary C-fiber afferents.

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REFERENCES


